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FILE LAST UPDATED: 13 Feb 1998 (980213/ED)

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=> s gossypol and cancer

```
          2302 GOSSYPOL
            25 GOSSYPOLS
          2303 GOSSYPOL
                 (GOSSYPOL OR GOSSYPOLS)
         81690 CANCER
          9807 CANCERS
         84652 CANCER
                 (CANCER OR CANCERS)
L1          24 GOSSYPOL AND CANCER
```

=> d 1-24 all l1

L1 ANSWER 1 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1997:472200 CAPLUS
DN 127:130588
TI **Gossypol** inhibition of mitosis, cyclin D1 and Rb protein in human mammary **cancer** cells and cyclin-D1 transfected human fibrosarcoma cells
AU Ligueros, M.; Jeoung, D.; Tang, B.; Hochhauser, D.; Reidenberg, M. M.; Sonenberg, M.
CS Departments of Pharmacology and Medicine, Cornell University Medical College, New York, NY, 10021, USA
SO Br. J. Cancer (1997), 76(1), 21-28
CODEN: BJCAAI; ISSN: 0007-0920
PB Churchill Livingstone
DT Journal
LA English
CC 1-6 (Pharmacology)
AB The antiproliferative effects of **gossypol** on human MCF-7 mammary **cancer** cells and cyclin D1-transfected HT-1060 human fibrosarcoma cells were investigated by cell cycle anal. and effects on the cell cycle regulatory proteins Rb and cyclin D1. Flow cytometry of MCF-7 cells at 24 h indicated that 10 .mu.m **gossypol** inhibited DNA synthesis by producing a G1/S block. Western blot anal. using anti-human Rb antibodies and anti-human cyclin D1 antibodies in MCF-7 cells and high- and low-expression cyclin D1-transfected fibrosarcoma cells indicated that, after 6 h exposure, **gossypol** decreased the expression levels of these proteins in a dose-dependent manner. **Gossypol** also decreased the ratio of phosphorylated to unphosphorylated Rb protein

in human mammary **cancer** and fibrosarcoma cell lines. **Gossypol** (10 .mu.M) treated also decreased cyclin D1-assocd. kinase activity on histone H1 used as a substrate in MCF-7 cells. These results suggest that **gossypol** might suppress growth by modulating the expression of cell cycle regulatory proteins Rb and cyclin D1 and the phosphorylation of Rb protein.

ST **gossypol** cyclin Rb protein mammary **cancer**; cell cycle protein **gossypol** fibrosarcoma antitumor

IT Breast tumor inhibitors
Cell cycle
Fibrosarcoma inhibitors
(**gossypol** inhibition of mitosis, cyclin D1, and Rb protein in human mammary and fibrosarcoma **cancer** cells)

IT Cyclin D1
Rb protein
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**gossypol** inhibition of mitosis, cyclin D1, and Rb protein in human mammary and fibrosarcoma **cancer** cells)

IT 303-45-7, **Gossypol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**gossypol** inhibition of mitosis, cyclin D1, and Rb protein in human mammary and fibrosarcoma **cancer** cells)

L1 ANSWER 2 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1997:356957 CAPLUS
DN 127:94530
TI Cows' milk fat components as potential anticarcinogenic agents
AU Parodi, Peter W.
CS Human Nutrition Program, Dairy R&D Corp., Glen Iris, Victoria, 3146, Australia
SO J. Nutr. (1997), 127(6), 1055-1060
CODEN: JONUAI; ISSN: 0022-3166
PB American Society for Nutritional Sciences
DT Journal; General Review
LA English
CC 18-0 (Animal Nutrition)
AB A review with ~50 refs. on the anticarcinogenic potential of several components of milk. The optimum approach to conquering **cancer** is prevention. Although the human diet contains components which promote **cancer**, it also contains components with the potential to prevent it. Recent research shows that milk fat contains a no. of potential anticarcinogenic components including conjugated linoleic acid, sphingomyelin, butyric acid and ether lipids. Conjugated linoleic acid inhibited proliferation of human malignant melanoma, colorectal, breast and lung **cancer** cell lines. In animals, it reduced the incidence of chem. induced mouse epidermal tumors, mouse forestomach neoplasia and aberrant crypt foci in the rat colon. In a no. of studies, conjugated linoleic acid, at near-phgysiol. concns., inhibited mammary tumorigenesis independently of the amt. and type of fat in the diet. In vitro studies showed that the milk phospholipid, sphingomyelin, through its biol. active metabolites ceramide and sphingosine, participates in three major antiproliferative pathways influencing oncogenesis namely, inhibition of cell growth, and induction of differentiation and apoptosis. Mice fed sphingomyelin had fewer colon tumors and aberrant crypt foci than control animals. About one third of all milk triacylglycerols contain one mol. of butyric acid, a potent inhibitor of proliferation and inducer of differentiation and apoptosis in a wide range of neoplastic cell lines. Although butyrate produced by colonic fermn. is considered important for colon **cancer** protection, and animal study suggests dietary butyrate may inhibit mammary tumorigenesis. The dairy cow also has

the ability to ext. other potential anticarcinogenic agents such as .beta.-carotene, .beta.-ionone and **gossypol** from its feed and transfer them to milk. Animal studies comparing the tumorigenic potential of milk fat or butter with linoleic acid-rich vegetable oils or margarines are reviewed. They clearly show less tumor development with dairy products.

ST milk fat cattle **cancer** review

IT Antitumor agents
Cattle
Cell proliferation
Milk
(cows' milk fat components as potential anticarcinogenic agents)

IT Fats and Glyceridic oils, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(cows' milk fat components as potential anticarcinogenic agents)

IT 60-33-3, Linoleic acid, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(cows' milk fat components as potential anticarcinogenic agents)

L1 ANSWER 3 OF 24 CAPLUS COPYRIGHT 1998 ACS

AN 1997:307389 CAPLUS

DN 126:338667

TI **Gossypol** arrests human benign prostatic hyperplastic cell growth at G0/G1 phase of the cell cycle

AU Shidaifat, Falah; Canatan, Halit; Kulp, Samuel K.; Sugimoto, Yasuro; Zhang, Yuan; Brueggemeier, Robert W.; Somers, William J.; Chang, William Y.; Wang, Hwa-Chain; Lin, Young C.

CS Laboratory of Reproductive and Molecular Endocrinology, College of Veterinary Medicine, The Ohio State University, Columbus, OH, 43210-1092, USA

SO Anticancer Res. (1997), 17(2A), 1003-1009
CODEN: ANTRD4; ISSN: 0250-7005

PB Anticancer Research

DT Journal

LA English

CC 1-10 (Pharmacology)

AB Recently we demonstrated that **gossypol** (GP), a male antifertility agent, is a potent inhibitor of malignant human prostate **cancer** cell growth that acts by arresting cells in G0/G1 phase and that this inhibitory effect may be mediated by transforming growth factor-.beta.1 (TGF-.beta.1). In this study we examd. the effect of GP on the growth of prostatic cells from human benign prostatic hyperplasia (BPH) patients in vitro. Consistent with its inhibitory effect on the growth of malignant human prostate **cancer** cells, GP also acts as a potent inhibitor of cultured human BPH cell growth as assessed by thymidine incorporation assay. These results were confirmed by flow cytometric anal. which revealed that treatment of human BPH cells with increasing concns. of GP resulted in a dose-dependent accumulation of cells in the G0/G1 phase with a concomitant decrease in cells progressing to the S and G2/M phases. Since inhibition of prostate **cancer** cells by GP appears to be mediated by TGF-.beta.1, we also investigated the effect of GP on TGF-.beta.1 gene expression in BPH cells. The results show that GP treatment resulted in a marked elevation of TGF-.beta.1 gene expression indicating that TGF-.beta.1 might be involved at least in part in the inhibitory pathway that is initiated by GP.

ST **gossypol** benign prostatic hyperplasia cell cycle; TGF betal **gossypol** benign prostatic hyperplasia

IT Prostatic hyperplasia
(benign; **gossypol** arrests human benign prostatic hyperplastic cell growth at G0/G1 phase of the cell cycle)

IT Cell cycle

(**gossypol** arrests human benign prostatic hyperplastic cell growth at G0/G1 phase of the cell cycle)

IT Genes (animal)
Transforming growth factor .beta.1
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**gossypol** arrests human benign prostatic hyperplastic cell growth at G0/G1 phase of the cell cycle)

IT 303-45-7, **Gossypol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**gossypol** arrests human benign prostatic hyperplastic cell growth at G0/G1 phase of the cell cycle)

L1 ANSWER 4 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1997:235254 CAPLUS
DN 126:287703
TI Differential regulation of gene expression by **gossypol**: a potential inhibitor of prostate cell growth (transforming growth factor, benign prostatic hyperplasia, tyrosine phosphatase)
AU Shidaifat, Falah Hasan
CS Ohio State Univ., Columbus, OH, USA
SO (1996) 161 pp. Avail.: Univ. Microfilms Int., Order No. DA9710657
From: Diss. Abstr. Int., B 1997, 57(10), 6097
DT Dissertation
LA English
CC 1-6 (Pharmacology)
AB Unavailable
ST **gossypol** prostate **cancer** cell cycle TGF
IT Prostatic hyperplasia
(benign; differential regulation of gene expression by **gossypol**, a potential inhibitor of prostate cell growth)
IT Cell cycle
Gene expression
Prostate
Prostatic tumor inhibitors
(differential regulation of gene expression by **gossypol**, a potential inhibitor of prostate cell growth)
IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(differential regulation of gene expression by **gossypol**, a potential inhibitor of prostate cell growth)
IT 303-45-7, **Gossypol**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(differential regulation of gene expression by **gossypol**, a potential inhibitor of prostate cell growth)
IT 79747-53-8, Protein tyrosine phosphatase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(differential regulation of gene expression by **gossypol**, a potential inhibitor of prostate cell growth)

L1 ANSWER 5 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1996:720737 CAPLUS
DN 126:14428
TI Inhibition of human prostate **cancer** cells growth by **gossypol** is associated with stimulation of transforming growth factor-.beta.
AU Shidaifat, Falah; Canatan, Halit; Kulp, Samuel K.; Sugimoto, Yasuro; Chang, William Y.; Zhang, Yuan; Brueggemeier, Robert W.; Somers, William J.; Lin, Young C.
CS Lab. Reproductive Molecular Endocrinol., Ohio State Univ., Columbus, OH, 43210-1092, USA
SO Cancer Lett. (Shannon, Irel.) (1996), 107(1), 37-44

CODEN: CALEDQ; ISSN: 0304-3835
PB Elsevier
DT Journal
LA English
CC 1-6 (Pharmacology)
AB **Gossypol** (GP), an antifertility agent in males, is also capable of inhibiting the proliferation of a wide range of **cancer** cells in vivo and in vitro. Thus, in this study we investigated the effect of GP on the growth of human androgen-independent prostate **cancer** cell line (P3). The results showed that GP acts as a potent inhibitor of PC3 cells as detd. by thymidine incorporation assay and flow cytometric anal. Flow cytometry revealed that treatment of PC3 cells with GP resulted in a dose- and time-dependent accumulation of cells in the GO/G1 phase with a concomitant decrease in cells progressing to the S and G2/M phases. These data support our thymidine incorporation results which indicated that GP is a potent inhibitor of PC3 cells. By RNase protection assay, we also investigated the effect of GP on transforming growth-factor-.beta.1 (TGF-.beta.1) gene expression in PC3 cells. Interestingly, the stimulatory effect of GP on TGB-.beta.1 gene expression correlates well with its inhibitory effect on PC3 cell DNA synthesis and its ability to arrest cells in GO/G1 phase. Based on these data, it can be concluded that GP is a potent inhibitor of prostate **cancer** cell growth that acts by arresting cells in GO/G1 phase and that this inhibitory effect may be mediated by TGF-.beta.1.
ST **gossypol** prostate **cancer** TGFb cell cycle
IT Cell cycle
(GO/G1 phase; **gossypol** inhibition of human prostate **cancer** mediation by transforming growth factor-.beta.)
IT Genes (animal)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(Tgfb-1; **gossypol** inhibition of human prostate **cancer** mediation by transforming growth factor-.beta.)
IT Prostatic tumor inhibitors
(androgen-independent; **gossypol** inhibition of human prostate **cancer** mediation by transforming growth factor-.beta.)
IT Transforming growth factors .beta.
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**gossypol** inhibition of human prostate **cancer** mediation by transforming growth factor-.beta.)
IT 303-45-7, **Gossypol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**gossypol** inhibition of human prostate **cancer** mediation by transforming growth factor-.beta.)

L1 ANSWER 6 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1996:321645 CAPLUS
DN 125:32121
TI Milk fat components: possible chemopreventive agents for **cancer** and other diseases
AU Parodi, P.W.
CS Dairy Research and Development Corporation, Glen Iris, 3146, Australia
SO Aust. J. Dairy Technol. (1996), 51(1), 24-32
CODEN: AJDTAZ; ISSN: 0004-9433
DT Journal; General Review
LA English
CC 17-0 (Food and Feed Chemistry)
AB A review with many refs. Milk fat contains a no. of components such as sphingomyelin, conjugated linoleic acid, butyric acid, ether lipids, vitamin A, .beta.-carotene and vitamin D which have the

potential to inhibit the process of carcinogenesis. Some also possess antiatherogenic and immunomodulating properties and may be beneficial in preventing other degenerative diseases. This review examines animal studies, human and animal cell culture studies, mechanisms, and other relevant evidence which supports this contention. To ascertain if benefit is in fact derived from these components, available evidence from animal models of colon, mammary, and skin tumorigenesis which compared the tumorigenic potential of linoleic acid-rich vegetable oils and margarine with milk fat and butter was examd. Compared with linoleic acid-rich vegetable oils and margarine, milk fat and butter inhibit tumorigenesis. The potential for the dairy cow to ext. potent chemopreventive substances from pasture and feedstuff and transfer them to milk for human consumption is discussed. As an example .beta.-ionone from lucerne has anticarcinogenic properties and may play a role in lowering blood cholesterol levels. **Gossypol** from cottonseed meal and genistein from soybean meal both act as anticarcinogenic agents.

ST review milk fat component antitumor

IT Neoplasm inhibitors
(milk fat components as chemopreventive agents for **cancer** and other diseases)

IT Fats and Glyceridic oils
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); FFD (Food or feed use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(milk, milk fat components as chemopreventive agents for **cancer** and other diseases)

L1 ANSWER 7 OF 24 CAPLUS COPYRIGHT 1998 ACS

AN 1995:604643 CAPLUS

DN 123:462

TI Antiproliferative activity of **gossypol** and gossypolone on human breast **cancer** cells

AU Gilbert, Nancy E.; O'Reilly, Jill E.; Chang, C. J. George; Lin, Young C.; Brueggemeier, Robert W.

CS Coll. Pharmacy, Ohio State Univ., Columbus, OH, 43210, USA

SO Life Sci. (1995), 57(1), 61-7
CODEN: LIFSAK; ISSN: 0024-3205

DT Journal

LA English

CC 1-6 (Pharmacology)
Section cross-reference(s): 2

AB **Gossypol** is a polyphenolic aldehyde occurring naturally in cottonseed that produces antisteroidogenic activity in vivo, has been extensively investigated as a male contraceptive agent, and has demonstrated anticancer activity. Gossypolone, the major metabolite of **gossypol**, also possesses antisteroidogenic activity but has not been examd. for its anticancer properties. The objectives of these investigations are to compare the effects of gossypolone with those of **gossypol** on cell proliferation of hormone-dependent and hormone-independent human breast carcinoma cells, i.e., MCF-7, MCF-7Adr and MDA-MB-231 cells. **Gossypol** and gossypolone were examd. at concns. up to 10 .mu.M, and cellular DNA synthesis was monitored by 3H-thymidine incorporation. **Gossypol** and gossypolone produced dose-dependent suppression of DNA synthesis in all of the human breast cell lines examd. **Gossypol** produced potent antiproliferative activity in MCF-7 cells at doses as low as 30 nM. Co-incubation of MCF-7 cells with **gossypol** (5 .mu.M) and estradiol (10 nM) did not alter the effects of **gossypol**. Treatment of human breast **cancer** cells with 2.5 .mu.M of **gossypol** resulted in alterations in cell shape and attachment to the surface of the culture dishes. At **gossypol** doses of 10 .mu.M, pericytoplasmic globuation and cytoplasmic swelling were obsd. in

the majority of breast **cancer** cells. These changes in cellular morphol. indicate a loss of ability of the cells to maintain normal cell membrane permeability, resulting in subsequent disorganization and loss of cytoplasmic organelles. Gossypolone is less potent than **gossypol** in producing these effects in the human breast **cancer** cell lines, whereas it possesses equipotent antisteroidogenic and antireproductive activities with **gossypol**. These investigations suggest that **gossypol** and **gossypol** analogs may have therapeutic potential for human breast **cancer**.

ST antiproliferative **gossypol** gossypolone breast **cancer**

IT Animal tissue culture
Cell morphology
Cell proliferation
Deoxyribonucleic acid formation
(antiproliferative activity of **gossypol** and gossypolone on human breast **cancer** cells)

IT Neoplasm inhibitors
(mammary gland carcinoma, antiproliferative activity of **gossypol** and gossypolone on human breast **cancer** cells)

IT Mammary gland
(neoplasm, carcinoma, inhibitors, antiproliferative activity of **gossypol** and gossypolone on human breast **cancer** cells)

IT 303-45-7, **Gossypol** 4547-72-2, Gossypolone
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiproliferative activity of **gossypol** and gossypolone on human breast **cancer** cells)

L1 ANSWER 8 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1995:344883 CAPLUS
DN 122:123198
TI Male contraception: hormonal, mechanical and other
AU Comhaire, Frank H.
CS Department of Internal Medicine, University Hospital Ghent, Ghent, 9000, Belg.
SO Hum. Reprod. (1994), 9(Suppl. 2 New Concepts in Fertility Control), 22-7
CODEN: HUREEE; ISSN: 0268-1161
DT Journal; General Review
LA English
CC 2-0 (Mammalian Hormones)
AB A review, with 47 refs., on methods of male contraception. Those that have been developed so far have mainly focused on the inhibition of spermatogenesis through suppression of the hypothalamo-pituitary secretion of gonadotrophins, and simultaneous supplementation with androgens. These methods include the use of combinations of progestogens or LH-releasing hormone antagonists and testosterone derivs., or high dose testosterone. Though effective contraception can be obtained, side-effects and/or the high cost of treatment limit the widespread use of these approaches. Inhibition of sperm maturation in the epididymis, or direct interference with spermatogenic cells or the cells of Sertoli by e.g. **gossypol** have been abandoned because of toxic side-effects. Voluntary sterilization by vasectomy is the most commonly used method of male contraception, but its surgical nature, problematic reversibility and suspected link with subsequent prostate **cancer** render the method far from ideal. Non-surgical vas occlusion may overcome some of these problems, but data on long-term side-effects and reversibility are lacking. New contraceptive developments should focus on interfering with highly specific aspects of spermatogenesis such as unique enzymic processes and intercellular communication through cytokines, or application of antibodies against antigens of

the epididymis or the spermatozoa. Only through better understanding of normal and pathol. spermatogenesis will it be possible to develop an acceptable male contraceptive.
ST review male contraception
IT Contraceptives
(male)

L1 ANSWER 9 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1995:231727 CAPLUS
DN 122:23356
TI Presence of antitumor activities in the milk collected from **gossypol**-treated dairy cows
AU Hu, Yun-Fu; Chang, Ching-Jey G.; Brueggemeier, Robert W.; Lin, Young C.
CS Laboratory of Reproductive Endocrinology, Department of Veterinary Physiology and Pharmacology, College of Veterinary Medicine, The Ohio State University, 1900 Coffey Road, Columbus, OH, 43210-1092, USA
SO Cancer Lett. (Shannon, Irel.) (1994), 87(1), 17-23
CODEN: CALEDQ; ISSN: 0304-3835
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 18
AB Two human breast carcinoma cell lines (MCF-7, MCF-7 Adr) and a rat esophageal **cancer** cell line (RE-B2T) were used to evaluate the antiproliferative potential of **gossypol** (GP)-contg. milk (GP-Milk), which was collected from Brown Swiss dairy cows treated daily with federally allowable 450 ppm of GP for 6 days. Treatment of the cultured **cancer** cells with GP-Milk for 24 h significantly inhibited the rates of 3H-thymidine incorporation during the ensuing 3-h period in all three tumorigenic cell lines. The inhibitory effects of GP-Milk occurred in a dose-dependent manner in all cases, but the calcd. ED50 varied with cell lines. ED50 for GP-Milk was estd. at 10% for wild-type MCF-7 human breast **cancer** cells, 15% for multidrug-resistant MCF-7 Adr human breast **cancer** cells and 50% for RE-B2T rat esophageal carcinoma cells. The potential of GP-Milk as a dietary supplement for the prevention and/or treatment of human breast **cancer** is discussed in this paper.
ST antitumor **gossypol** milk
IT Milk
Neoplasm inhibitors
(antitumor activities in milk from **gossypol**-treated dairy cows)
IT 303-45-7, **Gossypol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activities in milk from **gossypol**-treated dairy cows)

L1 ANSWER 10 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1995:188223 CAPLUS
DN 122:45830
TI Effects of acetate **gossypol**, high energy shock waves (HESW) and their combination on the human bladder **cancer** cell line BT5637
AU Xia, Hong; Zhang, Jingbo; Xai, Ming; Zang, Meifu
CS Inst. Basic med. Sci., Chinese Acad. Med. Sci., Beijing, 100005, Peop. Rep. China
SO Jiepou Xuebao (1994), 25(3), 291-7
CODEN: CPHPA5; ISSN: 0529-1356
DT Journal
LA Chinese
CC 1-6 (Pharmacology)

AB The growth potential of human bladder **cancer** cell line BT5637 was inhibited by acetate **gossypol** or HESW and more greatly by their combination as shown by the cell growth curve, mitosis index, and colony-forming rate. The growth curve showed that the effects of **gossypol** were reversible and related to the duration of action and the concn. of the drug. Exposure to HESW resulted in a temporal growth delay. 3H-TdR incorporation test and measurement of DNA content by a microspectrophotometer showed that **gossypol** or HESW and their combination exerted their action on DNA synthesis. Treatment with **gossypol** and HSEW or both also resulted in a percentage change of the cell nos. in G0/G1, S, or M phases as detd. by flow cytometry. It is suggested that **gossypol** could block cells from G0/G1 phase to S phase, and HESW perhaps inhibited S phase. Electron microscopic study showed that the ultrastructural changes produced by **gossypol**, HESW, or both manifested themselves in several aspects. The prominent changes were the swelling of mitochondria as well as vesiculation of endoplasmic reticulum. Northern blot results indicated that the expression of the C-myc gene was inhibited by acetate **gossypol** and the growth of BT5637 cells was probably assocd. with C-myc gene expression. Taking all the data mentioned above, the expt. demonstrated that acetate **gossypol** or HESW could inhibit cell growth, while the combination of the 2 agents might have a synergistic effect on the bladder **cancer** cells.

ST **gossypol** shock wave bladder **cancer** human

IT Shock wave
(acetate **gossypol** and high energy shock waves and their combination effect on human bladder **cancer** cell line BT5637)

IT Bladder
(neoplasm, acetate **gossypol** and high energy shock waves and their combination effect on human bladder **cancer** cells)

IT 303-45-7, **Gossypol**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(acetate **gossypol** and high energy shock waves and their combination effect on human bladder **cancer** cell line BT5637)

L1 ANSWER 11 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1994:69594 CAPLUS
DN 120:69594
TI Methods for inhibiting the proliferation of brain and hepatic metastases by using lonidamine, radiation, and heat
IN Kim, Jae H.; Kim, Sang H.; Alfieri, Alan; Young, Charles W.
PA Sloan-Kettering Institute for Cancer Research, USA
SO U.S., 26 pp. Cont. of U.S. Ser. No. 526,516, abandoned.
CODEN: USXXAM
PI US 5260327 A 931109
AI US 92-925813 920804
PRAI US 85-783209 851002
US 90-526516 900521
DT Patent
LA English
IC ICM A61K031-415
ICS A61K031-11
NCL 514405000
CC 1-6 (Pharmacology)
Section cross-reference(s): 8
AB The proliferation of brain or hepatic metastases is inhibited in vivo by administering lonidamine to enhance the sensitivity of the metastases to a subsequent application of heat and radiation, then applying heat (to raise the temp. of the metastases >41.degree.) and radiation (15-65 Gy). The heat and radiation are applied

concurrently or the radiation is applied subsequent to the application of heat. Mice with transplanted Meth-A fibrosarcomas were treated with lonidamine, radiation therapy, and hyperthermia at 41.2 or 41.7.degree..

ST lonidamine brain liver metastasis inhibitor; hyperthermia sensitizer lonidamine metastasis inhibitor; radiosensitizer lonidamine brain liver metastasis inhibitor; heat radiation lonidamine metastasis inhibition

IT Radiotherapy
(in brain and liver metastases inhibition with lonidamine and heat)

IT Fever and Hyperthermia
(in brain and liver metastases inhibition with lonidamine and radiation)

IT Radiosensitizers, biological
(lonidamine as hyperthermic sensitizer and, in brain and liver metastases inhibition)

IT Neoplasm inhibitors
(brain, metastasis, lonidamine and heat and radiation combination as)

IT Temperature effects, biological
(heat, in brain and liver metastases inhibition with lonidamine and radiation)

IT Neoplasm inhibitors
(liver, metastasis, lonidamine and heat and radiation combination as)

IT Brain, neoplasm
Liver, neoplasm
(metastasis, inhibitors, lonidamine and heat and radiation combination as)

IT 303-45-7, **Gossypol** 62669-70-9, Rhodamine 123
RL: BIOL (Biological study)
(as hyperthermic sensitizer of human **cancer** cells)

IT 50264-69-2, Lonidamine
RL: BIOL (Biological study)
(brain and liver metastases inhibition with heat and radiation and)

IT 98-92-0, Nicotinamide
RL: BIOL (Biological study)
(**cancer** inhibition with heat and radiation and)

IT 50-99-7, Glucose, miscellaneous
RL: MSC (Miscellaneous)
(**gossypol** effect on **cancer** cells deprived of)

L1 ANSWER 12 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1994:23190 CAPLUS
DN 120:23190
TI **Gossypol** inhibits basal and estrogen-stimulated DNA synthesis in human breast carcinoma cells
AU Hu, Y. F.; Chang, C. J. G.; Brueggemeier, R. W.; Lin, Y. C.
CS Coll. Vet. Med., Ohio State Univ., Columbus, OH, 43210-1092, USA
SO Life Sci. (1993), 53(25), PL433-PL438
CODEN: LIFSAK; ISSN: 0024-3205
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 2
AB Estrogen stimulates the growth of hormone-dependent human breast **cancer**. Failure of chemotherapy frequently results from the development of multidrug resistance. **Gossypol** (GP), a naturally occurring toxin, inhibits the growth of various carcinoma cells. Thus, the effects of GP on 17.beta.-estradiol (E2)-stimulated DNA synthesis were studied in 2 hormone-dependent human breast carcinoma cell lines: the wild-type MCF-7 and the multidrug-resistant MCF-7 Adr cells. Cells (5 .times. 104/well)

were cultured for 24 h in a chem.-defined, serum-free medium consisting of 1:1 mixt. of Dulbecco's Modified Eagle's medium and Ham's nutrient mixt. F12 (DMEM/F12) supplemented with insulin (5.0 .mu.g/mL), transferrin (5.0 .mu.g/mL), epidermal growth factor (EGF; 10.0 ng/mL), and antibiotics. E2 (0 or 10.0 nM), GP (0, 2.5, 5.0, 10.0 or 20.0 .mu.M) and bovine serum albumin (BSA; 0 or 0.1 mg/mL) were used as treatments in factorial exptl. design. Cells were treated for 24 h and finally pulsed with [3H]thymidine (5.0 .mu.Ci/mL) for 3 h. E2 significantly stimulated [3H]thymidine incorporation in both MCF-7 and MCF-7 Adr cells. GP at 10.0 and 20.0 .mu.M inhibited both basal and E2-stimulated DNA synthesis in human breast **cancer** cells. The inhibitory effects of GP at 10.0 .mu.M, but not at 20.0 .mu.M, were blocked by BSA treatment. Results from the present study indicate that GP treatment was antiproliferative in both drug-sensitive and multidrug-resistant **cancer** cells and that the antiproliferative effects of GP on human breast **cancer** cells were mediated through mechanisms independent of estrogenic responses. Thus, GP could be potentially very useful for treatment of human breast **cancer** patients, esp. those who have developed multidrug resistance.

ST **gossypol** neoplasm inhibitor breast **cancer**; estrogen **gossypol** mammary neoplasm

IT Deoxyribonucleic acid formation
(by mammary carcinoma cells, **gossypol** inhibition of)

IT Estrogens
RL: BIOL (Biological study)
(mammary carcinoma cell proliferation stimulated by, **gossypol** effect on)

IT Cell proliferation
(of mammary carcinoma cells, **gossypol** inhibition of)

IT Neoplasm inhibitors
(mammary gland carcinoma, **gossypol** as)

IT Mammary gland
(neoplasm, carcinoma, inhibitors, **gossypol** as)

IT 303-45-7, **Gossypol**
RL: BIOL (Biological study)
(mammary carcinoma cell proliferation inhibition by)

IT 50-28-2, 17.beta.-Estradiol, biological studies
RL: BIOL (Biological study)
(mammary carcinoma cell proliferation stimulated by, **gossypol** effect on)

L1 ANSWER 13 OF 24 CAPLUS COPYRIGHT 1998 ACS

AN 1993:225136 CAPLUS

DN 118:225136

TI Antiproliferative and antimetastatic effects of **gossypol** on Dunning prostate cell-bearing Copenhagen rats

AU Chang, C. J. G.; Ghosh, P. K.; Hu, Y. F.; Brueggemeier, R. W.; Lin, Y. C.

CS Coll. Vet. Med., Ohio State Univ., Columbus, OH, 43210-1092, USA

SO Res. Commun. Chem. Pathol. Pharmacol. (1993), 79(3), 293-312
CODEN: RCOCB8; ISSN: 0034-5164

DT Journal

LA English

CC 1-6 (Pharmacology)

AB **Gossypol**, a polyphenolic aldehyde naturally present in cottonseed, has long been recognized as a male contraceptive and recently as a potential anticancer agent. Our study used a rodent model to evaluate **gossypol**'s potential for the treatment of human prostatic carcinoma. Two-month-old Copenhagen male rats received s.c. implants of a subpassage of MAT-LyLu prostatic **cancer** line, a highly metastatic, androgen-independent Dunning prostate tumor subline that specifically metastasizes to lymph nodes and lungs of recipients. After 2 wk of **gossypol** treatment (0 or 12.5 mg/kg B.W./day s.c.) initiated immediately

after transplantation, the rats were sacrificed and evaluated for prostate tumor growth and metastasis. Testosterone and **gossypol** levels in tumor tissue and various reproductive organs and serum potassium level were measured by RIA, HPLC and at. emission spectroscopy (AES), resp. **Gossypol**-treated rats exhibited wt. redns. in developed MAT-LyLu prostate tumor mass and prostate of 24% ($p<0.05$) and 31% ($p<0.05$), resp.; whereas testicular and epididymal wts. were not significantly affected. Few metastases (20%) were obsd. in either lymph nodes or lungs of **gossypol** -treated recipients. The control rats, however, had a much higher rate of lung (60%) and lymph node metastasis (40%). Testicular testosterone levels, as measured by RIA, were significantly lower in **gossypol**-treated rats than in controls ($p<0.05$), but serum testosterone levels were not different. Extractable **gossypol** content in the prostate tumor, as measured by HPLC, reached 19.67 ng/gm and was 1.28 times higher than in liver, 1.98 times higher than in testes, but was 3.3% of that in prostate. Moreover, serum had the highest **gossypol** content (10.7 .mu.g/mL). Serum potassium levels, as measured by AES, were significantly higher in **gossypol**-treated individuals than controls ($p<0.05$). Our results indicate for the first time that **gossypol** has antiproliferative and antimetastatic effects on MAT-LyLu prostate **cancer** cells and can be explored as a potential therapeutic agent for androgen-independent human prostatic carcinoma.

ST **gossypol** antitumor antimetastatic prostate carcinoma

IT Liver, metabolism
Testis, metabolism
(**gossypol** accumulation in, after treatment of prostate carcinoma)

IT Neoplasm inhibitors
(metastasis, **gossypol** as, in prostate carcinoma)

IT Prostate gland
(neoplasm, carcinoma, inhibitors, **gossypol** as)

IT Neoplasm inhibitors
(prostate gland carcinoma, **gossypol** as)

IT 58-22-0, Testosterone
RL: BIOL (Biological study)
(**gossypol** decrease of, prostate carcinoma inhibition in relation to)

IT 303-45-7, **Gossypol**
RL: BIOL (Biological study)
(prostate carcinoma inhibition by)

L1 ANSWER 14 OF 24 CAPLUS COPYRIGHT 1998 ACS

AN 1992:143386 CAPLUS

DN 116:143386

TI Effects of **gossypol** on the cell cycle phases in T-47D human breast **cancer** cells

AU Thomas, Michael; Von Hagen, victoria; Moustafa, Yehia; Montmasson, Marie Paule; Monet, Jean Dominique

CS Lab. TIM3, Univ. Joseph Fourier, Grenoble, F-38041, Fr.

SO Anticancer Res. (1991), 11(4), 1469-75
CODEN: ANTRD4; ISSN: 0250-7005

DT Journal

LA English

CC 1-6 (Pharmacology)
Section cross-reference(s): 2

AB Since **gossypol**, a naturally occurring component of cottonseed oil, exhibits a broad spectrum of activities, the authors have examd. it as an antitumor agent on breast **cancer**. The effects of different concns. of **gossypol** on the T-47D human breast **cancer** cell cycle phases were studied using cytometric image processing on Feulgen stained nuclei. The proportion of cells at different cell cycle phases was detd. by

discriminate anal. of the image parameters and gave good classification ranging from 86 to 100%. **Gossypol** was found to increase the G0/G1 fraction of the T-47D cells. This cell kinetic alteration by **gossypol** was shown to be dose dependent and reversible. Complete reversal of the effect of **gossypol** was obsd. after four days with a simple change to **gossypol**-free medium. The cell then progressed into S and G2/M phase, thus indicating that **gossypol**-treated cells remain viable. **Gossypol** was shown to have a strong inhibitory effect on cellular proliferation in T-47D cells. It was also found that this agent is only toxic to cells at the highest dose tested (10 .mu.M). The results of this study may be of clin. significance in the treatment of breast **cancer**, since **gossypol** shows strong antiproliferative properties.

ST **gossypol** breast **cancer** cell cycle phase

IT Cell cycle
(in T-47D human breast **cancer** cells, **gossypol** effect on)

IT Neoplasm inhibitors
(mammary gland adenocarcinoma, **gossypol**, in humans, cell cycle phases response to)

IT Mammary gland
(neoplasm, adenocarcinoma, inhibitors, **gossypol**, in humans, cell cycle phases response to)

IT 303-45-7, **Gossypol**
RL: BIOL (Biological study)
(cell cycle phases in T-47D human breast **cancer** cells response to)

L1 ANSWER 15 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1991:485409 CAPLUS
DN 115:85409
TI **Gossypol** and related compounds for the treatment of **cancer**
IN Flack, Mary R.; Knazek, Richard; Reidenberg, Marcus
PA National Institutes of Health, USA
SO U. S. Pat. Appl., 20 pp. Avail. NTIS Order No. PAT-APPL-7-551 353.
CODEN: XAXXAV
PI US 551353 A0 910415
AI US 90-551353 900712
DT Patent
LA English
CC 1-6 (Pharmacology)

AB **Gossypol** (I) and related compds. are provided as antitumor agents effective against human **cancers**. In a study of the effect of I on SW-13 tumor-bearing nude mice, tumor prevalence had dropped from 71 to 54% after 12 wk in the treatment group, while tumor prevalence had risen in the control group; there was no significant effect on body wts. During the study period, 8.3 and 41.6%, resp., of I-treated and control animals died. Preliminary results of I treatment in a clin. trial with metastatic adrenocortical carcinoma patients are also given.

ST **gossypol** neoplasm inhibitor; metastatic adrenocortical carcinoma inhibitor **gossypol**

IT Neoplasm inhibitors
(**gossypol**)

IT Adrenal cortex, neoplasm
(carcinoma, treatment of, with **gossypol**)

IT Neoplasm inhibitors
(carcinoma, metastasis, adrenocortical, **gossypol**)

IT 303-45-7, **Gossypol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoplasm inhibitor)

L1 ANSWER 16 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1991:135705 CAPLUS
DN 114:135705
TI Modulation of resistance to alkylating agents in **cancer** cell by **gossypol** enantiomers
AU Ford, J. M.; Hait, W. N.; Matlin, S. A.; Benz, C. C.
CS Sch. Med., Yale Univ., New Haven, CT, 06510, USA
SO Cancer Lett. (Shannon, Irel.) (1991), 56(1), 85-94
CODEN: CALEDQ; ISSN: 0304-3835
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Several cell lines resistant to alkylating agents possess increased activity to gluthathione-S-transferase (GST) drug detoxifying enzymes. Inhibition of certain enzymes of the gluthathione redox system may affect cellular sensitivity to alkylators. The authors report that the (-)enantiomer of **gossypol** is a potent and selective inhibitor of GST.alpha. and GST.pi. isoenzymes, and that in combination with buthionine sulfoximine (BSO), causes the enhanced modulation of alkylator resistance in two drug resistant cell lines with increased GST activity. The use of (-) **gossypol** alone had no effect on the 2-5-fold resistance of MCF-7 Adr and Walker resistant cells to chlorambucil, melphalan, and BCNU. Cellular depletion of glutathione with BSO resulted in a 2-4-fold modulation of cell sensitivity to these alkylators. However, the combination of (-)**gossypol** with BSO resulted in a markedly greater modulation of alkylator sensitivity than with either inhibitor alone. Therefore, the complementary inhibition of glutathione and GST by BSO and (-)**gossypol**, resp., produced a synergistic modulation of alkylator cytotoxicity in these drug resistant cell lines. The favorable clin. pharmacokinetics of (-)**gossypol** suggest its further evaluation for use in combination with BSO and alkylating agents in clin. trials.
ST **gossypol** alkylating agent resistance antitumor; buthionine sulfoximine antitumor resistance **gossypol**
IT Neoplasm inhibitors
(alkylating agents as, resistance to, in tumor cells, (-)-**gossypol** modulation of, buthionine sulfoximine synergism in)
IT Alkylating agents, biological
(resistance to, in tumor cells, (-)-**gossypol** modulation of, buthionine sulfoximine synergism in)
IT Drug resistance
(to antitumor alkylating agents, (-)-**gossypol** modulation of, buthionine sulfoximine synergism in)
IT 20300-26-9, (+)-**Gossypol**
RL: BIOL (Biological study)
(glutathione-S-transferase isoenzymes and resistant tumor cells growth inhibition by)
IT 70-18-8, Glutathione, biological studies
RL: BIOL (Biological study)
(**gossypol** and buthionine sulfoximine inhibition of, antitumor resistance modulation in relation to)
IT 5072-26-4, Buthionine sulfoximine
RL: BIOL (Biological study)
(resistance to antitumor alkylating agents modulation by (-)-**gossypol** and, mechanism of)
IT 90141-22-3, (-)-**Gossypol**
RL: BIOL (Biological study)
(resistance to antitumor alkylating agents modulation by buthionine sulfoximine and, mechanism of)
IT 148-82-3, Melphalan 154-93-8, BCNU 305-03-3, Chlorambucil 15663-27-1, Cisplatin
RL: BIOL (Biological study)
(resistance to, in tumor cells, (-)-**gossypol** modulation

of, buthionine sulfoximine synergism in)
IT 50812-37-8, Glutathione-S-transferase
RL: BIOL (Biological study)
(.alpha. and .mu. and .pi. isoenzymes, **gossypol** enantiomers inhibition of, antitumor resistance modulation in relation to)

L1 ANSWER 17 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1991:291 CAPLUS
DN 114:291
TI Action of **gossypol** and rhodamine 123 on wild type and multidrug-resistant MCF-7 human breast **cancer** cells: phosphorus-31 nuclear magnetic resonance and toxicity studies
AU Jaroszewski, Jerzy W.; Kaplan, Ofer; Cohen, Jack S.
CS Biophys. Pharmacol. Sect., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Cancer Res. (1990), 50(21), 6936-43
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
CC 1-6 (Pharmacology)
AB The action of **gossypol**, a polyphenolic bisnaphthalene aldehyde, on a no. of drug-sensitive and multidrug-resistant cell lines, in particular MCF-7 WT and MCF-7 ADR cells, was studied and compared to the effects of rhodamine 123. 31P-NMR spectra of cells exposed to low concns. of **gossypol** exhibited decreased levels of ATP, markedly increased levels of pyridine nucleotides, and decreased levels of glycerylphosphocholine. The latter effect may be related to the membrane viscosity-increasing effect of **gossypol**, whereas changes in the levels of pyridine nucleotides are probably due to an interference with NAD- and NADP-dependent enzymes. The effect of **gossypol** represents a rare example of selective and differentiated changes obsd. in 31P NMR spectra of cells following exposure to a drug; the effect was markedly different from that of rhodamine 123, which caused ATP depletion but no changes in the levels of glycerylphosphocholine or pyridine nucleotides. Also, the effects of **gossypol** and rhodamine 123 on glucose metab. in the MCF-7 WT cells were different. Thus although both drugs caused a marked elevation of glucose uptake, an increase in lactate prodn. exceeding that of glucose consumption, indicating an inhibition of oxidative phosphorylation, was obsd. only in the case of rhodamine 123. Significantly, multidrug-resistant cells exhibited strong cross-resistance to rhodamine but practically no resistance to **gossypol**, which emphasizes the attractiveness of the latter as a potential anticancer drug. The resistance to rhodamine 123 and sensitivity to **gossypol** was also obsd. with cells transfected with the mdr1 gene, showing that the difference in toxicity is mainly due to the different response to the P-170 drug efflux pump.
ST **gossypol** rhodamine 123 antitumor multidrug resistance
IT Neoplasm inhibitors
(**gossypol** and rhodamine 123, cytotoxic mechanism of, multidrug resistance in relation to)
IT Cell membrane
(**gossypol** but not rhodamine 123 effect on viscosity of, decrease of glycerylphosphocholine in, in cytotoxic mechanism, multidrug resistance in relation to)
IT Nucleotides, biological studies
RL: BIOL (Biological study)
(**gossypol** but not rhodamine 123 increase of, interference with NAD- and NADP-dependent enzyme in, multidrug resistance in relation to)
IT Drug resistance
(multi-, to rhodamine 123 but not **gossypol**, cytotoxic

mechanism in relation to)

IT Phosphorylation, biological
(oxidative, **gossypol** and rhodamine 123 effect on, depletion of ATP in, multidrug resistance in relation to)

IT 62669-70-9, Rhodamine 123
RL: BIOL (Biological study)
(cytotoxic mechanism of **gossypol** vs., multidrug resistance in relation to)

IT 303-45-7, **Gossypol**
RL: BIOL (Biological study)
(cytotoxic mechanism of rhodamine 123 vs., multidrug resistance in relation to)

IT 56-65-5, 5'-ATP, biological studies
RL: BIOL (Biological study)
(**gossypol** and rhodamine 123 depletion of, multidrug resistance in relation to)

IT 53-57-6, NADPH 53-59-8, NADP 53-84-9, NAD 58-68-4, NADH
RL: BIOL (Biological study)
(**gossypol** and rhodamine 123 effect on, multidrug resistance in relation to)

IT 563-24-6
RL: BIOL (Biological study)
(**gossypol** but not rhodamine 123 decrease of, multidrug resistance in relation to)

IT 50-99-7, Glucose, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, **gossypol** and rhodamine 123 effect on, multidrug resistance in relation to)

L1 ANSWER 18 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1990:490941 CAPLUS
DN 113:90941
TI Biochemical correlates of the antitumor and antimitochondrial properties of **gossypol** enantiomers
AU Benz, Christopher C.; Keniry, Max A.; Ford, James M.; Townsend, Alan J.; Cox, Fred W.; Palayoor, Sanjeewani; Matlin, Stephen A.; Hait, William N.; Cowan, Kenneth H.
CS Dep. Pharm. Chem., Univ. California, San Francisco, CA, 94143, USA
SO Mol. Pharmacol. (1990), 37(6), 840-7
CODEN: MOPMA3; ISSN: 0026-895X
DT Journal
LA English
CC 1-3 (Pharmacology)
AB Racemic **gossypol** has antitumor properties that may be due to its ability to uncouple tumor mitochondria or to its inhibitory effects on nonmitochondrial enzymes. The antimitochondrial and enzyme-inhibiting properties of **gossypol** were studied in human carcinoma cell lines of breast (MCF-7, T47-D), ovarian (OVCAR-3), colon (HCT-8), and pancreatic (MiaPaCa) origin by comparing the effects of its purified (+)- and (-)-enantiomers. (-)-**Gossypol** had .ltoreq.10-fold greater antiproliferative activity than (+)-**gossypol** in the **cancer** cell lines and in normal hematopoietic stem cells grown in vitro, with IC50 values 1.5-4.0 .mu.M for the **cancer** cells and 10-20 .mu.M for the human marrow stem cells. Multidrug-resistant MCF/Adr cells were more resistant to (-)-**gossypol** than their parental cell line. The earliest ultrastructural change in tumor cells exposed to a cytotoxic (10 .mu.M) concn. of (-)-**gossypol** was a selective destruction of their mitochondria. Consistent with this observation, 31P-NMR detected pronounced changes in tumor cell high energy phosphate metab. within 24 h of (-)-**gossypol** treatment, with 1.6- to >50-fold differential redns. in the intracellular ratios of ATP/Pi, relative to (+)-**gossypol**-treated cell lines; the magnitude of these

antimitochondrial effects correlated with the antiproliferative activity of (-)-**gossypol**. Northern blot RNA analyses suggested that treatments with a 5-10 .mu.M dose of (-)-**gossypol** caused a transient increase in the expression of heat shock gene products, particularly hsp-70 transcripts. The mean 5-fold increase in (-)-**gossypol**-induced hsp-70 mRNA was coincident with a comparable heat-stimulated increase in transcript levels, as compared with control or (+)-**gossypol**-treated cells. The enzyme-inhibiting properties of **gossypol** enantiomers were compared in cell-free assays measuring glutathione S-transferase .alpha., .mu., and .pi. activities, calmodulin stimulation of cyclic nucleotide phosphodiesterase, and protein kinase C activity. Both enantiomers were almost equiv. antagonists of calmodulin stimulation and protein kinase C activity, exceeding the potency of known inhibitors such as phenothiazines by as much s 50-fold. In contrast, (-)-**gossypol** was a 3-fold more potent inhibitor of glutathione S-transferase .alpha. and .pi. isoenzyme activity, resulting in IC50 values of 1.6 and 7.0 .mu.M, resp., for these two isoenzymes. Because of the enhanced resistance of MCF/Adr cells to (-)-**gossypol**, which may be related to their increased glutathione S-transferase and protein kinase C content, (-)-**gossypol** should be evaluated for its potential to modify the cytotoxic resistance of human carcinoma cells to other chemotherapeutic agents. The effects of (+)- and (-)-**gossypol** may be useful in directing structure-function studies using chiral-specific **gossypol** derivs., in order to develop more selective and potent antimitochondrial chemotherapeutic agents.

ST **gossypol** enantiomer antitumor mitochondria enzyme structure

IT Neoplasm inhibitors
(**gossypol** enantiomers as, mitochondrial enzymes and phosphates response to)

IT Mitochondria
(**gossypol** enantiomers effects on enzymes and phosphate metab. in, antitumor activity in relation to)

IT Calmodulins
RL: BIOL (Biological study)
(**gossypol** enantiomers effects on, antitumor activity in relation to)

IT Ribonucleic acids, messenger
RL: BIOL (Biological study)
(heat-shock protein-specifying, **gossypol** enantiomers effects on, antitumor activity in relation to)

IT Proteins, specific or class
RL: BIOL (Biological study)
(hsp 70, **gossypol** enantiomers effects on, antitumor activity in relation to)

IT Molecular structure-biological activity relationship
(neoplasm-inhibiting, of **gossypol** enantiomers)

IT Molecular structure-biological activity relationship
(oxidative phosphorylation-uncoupling, of **gossypol** enantiomers)

IT 9026-43-1, Protein kinase
RL: BIOL (Biological study)
(C, **gossypol** enantiomers effects on, antitumor activity in relation to)

IT 20300-26-9, (+)-**Gossypol** 90141-22-3, (-)-**Gossypol**
RL: PRP (Properties)
(antitumor effects of, mitochondrial enzymes response to, structure in relation to)

IT 56-65-5, 5'-ATP, biological studies 14265-44-2, Phosphate, biological studies
RL: BIOL (Biological study)

(**gossypol** enantiomers effects on, antitumor activity in relation to)

IT 50812-37-8, Glutathione S-transferase
RL: BIOL (Biological study)
(isoenzymes of, **gossypol** enantiomers effects on, antitumor activity in relation to)

L1 ANSWER 19 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1989:624936 CAPLUS
DN 111:224936
TI The effect of **gossypol** and 6-aminonicotinamide on tumor cell metabolism: a phosphorus-31 magnetic resonance spectroscopic study
AU Keniry, Max A.; Hollander, Charlene; Benz, Christopher C.
CS Res. Sch. Chem., Aust. Natl. Univ., Canberra, 2601, Australia
SO Biochem. Biophys. Res. Commun. (1989), 164(2), 947-53
CODEN: BBRCA9; ISSN: 0006-291X
DT Journal
LA English
CC 1-6 (Pharmacology)
AB 31P-magnetic resonance spectroscopy has been used to assess the changes in the levels of water-sol. phosphate pools in T47-D breast carcinoma cells induced by the antimitochondrial drugs, **gossypol** and 6-aminonicotinamide. A decrease in the nucleoside triphosphates/inorg. phosphate (NTP/Pi) ratio accurred after treatment with **gossypol**. No change in the NTP-Pi ratio occurred on treatment with 6-aminoicotinamide; however, a substantial accumulation of 6-phosphogluconate was obsd. Pretreatment of T47-D cells with **gossypol** prevented the accumulation of 6-phosphogluconate. This facile and non-invasive approach suggests that the oxidative part of the pentose-phosphate shuttle is an important source of reducing equiv. in T47-D cells. This pathway may prove to be a useful target for site-directed drug attack in carcinoma cell lines that require large quantities of NADP for the synthesis of fatty acids and steroids.
ST **gossypol** aminonicotinamide tumor metab phosphorus MRS; magnetic resonance spectroscopy tumor antitumor drug
IT Phosphates, biological studies
RL: BIOL (Biological study)
(inorg., aminonicotinamide and **gossypol** effect on nucleoside triphosphates and, of human breast carcinoma cells)
IT Pentose phosphate pathway
(oxidative part of, of human breast carcinoma cells, aminonicotinamide effect on)
IT Neoplasm inhibitors
(carcinoma, aminonicotanimide and **gossypol** as, phosphate pools in human breast cells response to)
IT Mammary gland
(neoplasm, carcinoma, phosphate pools of human, aminonicotinamide and **gossypol** effect on, phosphorus-31 magnetic resonance spectroscopic study of)
IT Phosphorylation, biological
(oxidative, uncoupling of, in mitochondria of human breast carcinoma cells, by **gossypol** d)
IT Nucleotides, biological studies
RL: BIOL (Biological study)
(triphosphates, aminonicotinamide and **gossypol** effect on, inorg. phosphates and, of human breast carcinoma cells)
IT 921-62-0
RL: BIOL (Biological study)
(accumulation of, in human breast carcinoma cells, aminonicotinamide and **gossypol** effect on)
IT 53-59-8, NAD(P) 56-65-5, ATP, biological studies
RL: FORM (Formation, nonpreparative)
(formation of, aminonicotinamide and **gossypol** effect on

DN 110:51382
TI Determination of **gossypol** enantiomers in plasma after administration of racemate using high-performance liquid chromatography with precolumn chemical derivatization
AU Wu, Da Fang; Reidenberg, Marcus M.; Drayer, Dennis E.
CS Med. Coll., Cornell Univ., New York, NY, 10021, USA
SO J. Chromatogr. (1988), 433, 141-8
CODEN: JOCRAM; ISSN: 0021-9673
DT Journal
LA English
CC 2-1 (Mammalian Hormones)
AB A HPLC assay with precolumn chem. derivatization was developed for the detn. of **gossypol** enantiomers in plasma, after administration of the racemate. Racemic **gossypol** acetic acid in plasma was extd. into acetonitrile and analyzed using a reversed-phase column and a coulometric detector in the redox mode. To sep. the enantiomers, 30 .mu.L of the chiral derivatizing reagent, (R)-(-)-2-amino-1-propanol (50 mg/mL) and 15 .mu.L of 20% (vol./vol) acetic acid were added to the acetonitrile layer which was then heated at 60.degree. for 100 min. The mobile phase used to resolve the derivatized enantiomers was 0.2M phosphate buffer (pH 3.5)-acetonitrile (38:62, vol./vol.). At a flow rate of 1.5 mL/min, the retention times for derivatized (+)-**gossypol** and (-)-**gossypol** were 4.0 and 7.8 min, resp. Two **cancer** patients received 10 mg racemic **gossypol** acetic acid 3 times a day. In 1 patient, the racemic, (+)- and (-)-**gossypol** acetic acid plasma concns. after 65 days of therapy were 317, 213, and 104 ng/mL, resp. In the other patient, these values were 362, 210, and 152 ng/mL, resp., after a week of therapy.
ST **gossypol** enantiomer detn blood chromatog; HPLC
gossypol enantiomer blood analysis
IT Blood analysis
(**gossypol** enantiomers detn. in, of human by HPLC with precolumn derivatization)
IT 40112-23-0, (.+-.)-**Gossypol**
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in blood plasma of human by HPLC)
IT 20300-26-9, (+)-**Gossypol** 90141-22-3, (-)-**Gossypol**
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in blood plasma of human by HPLC with precolumn derivatization)
IT 115038-46-5
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmacokinetics of, in animal and human)

L1 ANSWER 22 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1983:499504 CAPLUS
DN 99:99504
TI The effect of the association of **gossypol** and lonidamine on the energy metabolism of Ehrlich ascites tumor cells
AU Floridi, A.; D'Atri, S.; Menichini, R.; Marcante, M. L.; Nista, A.; Silvestrini, B.; Caputo, A.; De Martino, C.
CS Regina Elena Inst. Cancer Res., Rome, 00161, Italy
SO Exp. Mol. Pathol. (1983), 38(3), 322-35
CODEN: EXMPA6; ISSN: 0014-4800
DT Journal
LA English
CC 2-3 (Mammalian Hormones)
Section cross-reference(s): 14
AB The action of **gossypol** [303-45-7] and lonidamine [50264-69-2] was studied on Ehrlich ascites tumor cells harvested from Swiss male mice. Low concns. of **gossypol** increased the rate of O consumption by uncoupling oxidative phosphorylation.

High concns. resulted in an inhibition of consumption with a mechanism not directly related to the uncoupling activity. **Gossypol**, at concns. at which it exerts an uncoupling activity, stimulated mitochondrial ATPase which in turn increased the aerobic and anaerobic rates of lactate prodn. The decrease of glycolysis at high concns. of **gossypol** did not depend on the inhibition of enzymes of the glycolytic pathway, but must be ascribed to cell death. The assocn. of a low concns. of **gossypol** with lonidamine brought about a further inhibition of consumption. Lonidamine abolished the stimulation of glycolysis induced by **gossypol** and lower lactate prodn. to values that are quite similar to those found with lonidamine alone. Evidently, the combined treatment of **gossypol** and lonidamine effectively decreases the energy requirements of **cancer** cells.

ST tumor energy metab **gossypol** lonidamine; glycolysis tumor **gossypol** lonidamine

IT Mitochondria
(ATPase of, of Ehrlich ascites tumor cell, **gossypol** and lonidamine effect on)

IT Animal respiration
(by Ehrlich ascites tumor cell, **gossypol** and lonidamine effect on)

IT Carcinoma
(Ehrlich ascites, energy metab. by, **gossypol** and lonidamine effect on)

IT 50264-69-2
RL: BIOL (Biological study)
(Ehrlich ascites tumor cell energy metab. in response to **gossypol** and)

IT 303-45-7
RL: BIOL (Biological study)
(Ehrlich ascites tumor cell energy metab. response to lonidamine and)

IT 50-21-5, biological studies
RL: FORM (Formation, nonpreparative)
(formation of, by Ehrlich ascites tumor cell, **gossypol** and lonidamine effect on)

IT 9000-83-3
RL: BIOL (Biological study)
(of mitochondria, of Ehrlich ascites tumor cell, **gossypol** and lonidamine effect on)

L1 ANSWER 23 OF 24 CAPLUS COPYRIGHT 1998 ACS

AN 1980:420463 CAPLUS

DN 93:20463

TI Hepatocarcinogenicity of glandless cottonseeds and cottonseed oil to rainbow trout (Salmo gairdnerii)

AU Hendricks, J. D.; Sinnhuber, R. O.; Loveland, P. M.; Pawlowski, N. E.; Nixon, J. E.

CS Dep. Food Sci. Technol., Oregon State Univ., Corvallis, OR, 97331, USA

SO Science (Washington, D. C.) (1980), 208(4441), 309-11
CODEN: SCIEAS; ISSN: 0036-8075

DT Journal

LA English

CC 4-7 (Toxicology)

AB Glandless cottonseed kernels contained no **gossypol** but still have a full complement of naturally occurring cyclopropenoid fatty acids, which in rainbow trout were active as synergists with aflatoxins and primary liver carcinogens. Diets contg. glandless cottonseed kernels or a lightly processed cottonseed oil produced nos. of hepatocellular carcinomas in rainbow trout after 1 yr. The much greater incidence of **cancer** induced by the kernel than by the oil indicated that synergists or other carcinogens may

be present in the kernel in addn. to the cyclopropenoid fatty acids.
ST Salmo cottonseed carcinogenicity liver; cottonseed carcinogenicity liver rainbow trout
IT Cottonseed oil
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(carcinogenicity of, to liver of rainbow trout)
IT Neoplasm
(from cottonseed, of liver of rainbow trout, oil in relation to)
IT Liver, neoplasm
(from cottonseed, of rainbow trout, oil in relation to)
IT Cottonseed
(glandless, carcinogenicity of, to liver of rainbow trout, oil in relation to)
IT Salmo gairdneri
(liver of, cottonseed carcinogenicity of, oil in relation to)

L1 ANSWER 24 OF 24 CAPLUS COPYRIGHT 1998 ACS
AN 1969:55288 CAPLUS
DN 70:55288
TI Dietary factors and hepatoma in rainbow trout (Salmo gairdneri). II.
AU Sinnhuber, Russell O.; Lee, Donald J.; Wales, J. H.; Ayres, J. L.
CS Oregon State Univ., Corvallis, Oreg., USA
SO J. Nat. Cancer Inst. (1968), 41(6), 1293-301
CODEN: JNCIAM
DT Journal
LA English
CC 9 (Nonmammalian Biochemistry)
AB Aflatoxin B1 (one of the toxic metabolites of the mold Aspergillus flavus) was fed in a semipurified exptl. diet to rainbow trout at levels of 4, 8, and 20 ppb. A logarithmic response in the incidence of tumors to dietary level of aflatoxin was found. Cyclopropenoid fatty acids fed at 220 ppm. in an aflatoxin-contg. diet increased the incidence and growth of hepatoma many-fold over the pos. control. **Gossypol** and 3-methylcoumarin did not promote the early development of the aflatoxin-induced tumors, but the incidence and size of tumor nodules were greater after 12 months. Heat-polymd. corn oil or oxidized salmon oil did not enhance the carcinogenicity of aflatoxin B1. Feeding a com. ration, which contained aflatoxin-contaminated cottonseed meal, for 2 weeks produced a hepatoma incidence of 60% after 9 months.
ST **cancer** aflatoxin trout; aflatoxin trout **cancer**; trout aflatoxin **cancer**; cyclopropenoid **gossypol** **cancer**; **gossypol** cyclopropenoid **cancer**
IT Salmo
(gairdnerii, hepatoma of, diet in relation to)
IT Liver, neoplasms
(lipid effect on, in Salmo gairdnerii)
IT Fatty acids, biological studies
RL: BIOL (Biological study)
(neoplasm formation by cyclopropenoid, in liver of Salmo gairdnerii)
IT Lipids
RL: BIOL (Biological study)
(neoplasm of liver in response to, in Salmo gairdnerii)
IT Neoplasms, responses to chemicals
(to lipids in liver of Salmo gairdnerii)
IT 1162-65-8
RL: BIOL (Biological study)
(neoplasm of liver from, carcinogens for)
IT 303-45-7
RL: BIOL (Biological study)
(neoplasm of liver in response to)

AN 1989:165719 CAPLUS
DN 110:165719
TI Antiproliferative effect of **gossypol** and its optical isomers on human reproductive **cancer** cell lines
AU Band, Vimla; Hoffer, Anita P.; Bands, Hamid; Rhinehardt, Ann E.; Knapp, Robert C.; Matlin, Stephen A.; Anderson, Deborah J.
CS Dana Farber Cancer Inst., Harvard Med. Sch., Boston, MA, 02115, USA
SO Gynecol. Oncol. (1989), 32(3), 273-7
CODEN: GYNOA3; ISSN: 0090-8258
DT Journal
LA English
CC 1-6 (Pharmacology)
Section cross-reference(s): 2
AB The antiproliferative effect of **gossypol** and its optical isomers on various human cell lines of reproductive and nonreproductive tissue origin was studied. Various reproductive **cancer** cell lines of ovarian, gestational, and testicular origin were highly sensitive (IC50 values of 0.86-1.98 .mu.g/mL) to **gossypol**. The antiproliferative action of **gossypol** was not restricted to reproductive **cancers**, as nonreproductive **cancer** cell lines were also equally sensitive (IC50 values of 0.69-3.55 .mu.g/mL). In addn., actively proliferating untransformed cells such as fibroblasts and PHA-activated lymphocytes were also sensitive (IC50 values of 0.87-2.51 .mu.g/mL). (-)-**Gossypol** was 3.6-12.4 times more potent than (+)-**gossypol** and 1.48-2.65 times more potent than (.+-.)-**gossypol**. The most sensitive indicator of **gossypol** action was a decrease in DNA synthesis, followed by inhibition of protein synthesis and uptake of rhodamine-123 by mitochondria, as tested in an ovarian **cancer** cell line (OVCA 433) and a fibroblast line (Hs27). **Gossypol** possesses a general nonselective antiproliferative action toward human cells in vitro. Further, the pharmacol. activity of **gossypol** as an antiproliferative agent is primarily attributable to its (-) isomer, which is also the active isomer as a contraceptive.
ST **gossypol** gonadal **cancer**; cell proliferation
gossypol isomer
IT Neoplasm inhibitors
(**gossypol** isomer as, for gonadal cells)
IT Cytotoxic agents
(**gossypol** isomers as)
IT 20300-26-9, (+)-**Gossypol** 40112-23-0, (.+-.)-**Gossypol** 90141-22-3, (-)-**Gossypol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoplasm inhibiting activity of, in gonadal **cancer**, cell proliferation inhibition in relation to)

AN 1989:165719 CAPLUS
DN 110:165719
TI Antiproliferative effect of **gossypol** and its optical isomers on human reproductive **cancer** cell lines
AU Band, Vimla; Hoffer, Anita P.; Bands, Hamid; Rhinehardt, Ann E.; Knapp, Robert C.; Matlin, Stephen A.; Anderson, Deborah J.
CS Dana Farber Cancer Inst., Harvard Med. Sch., Boston, MA, 02115, USA
SO Gynecol. Oncol. (1989), 32(3), 273-7
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ST **gossypol** gonadal **cancer**; cell proliferation
gossypol isomer
IT Neoplasm inhibitors
(**gossypol** isomer as, for gonadal cells)
IT Cytotoxic agents
(**gossypol** isomers as)
IT 20300-26-9, (+)-**Gossypol** 40112-23-0, (.+-.)-**Gossypol** 90141-22-3, (-)-**Gossypol**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoplasm inhibiting activity of, in gonadal **cancer**, cell proliferation inhibition in relation to)